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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,145	02/22/2002	Manja Ahola	TUR-125	7684

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	10/069,145	AHOLA ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☒ Claim(s) *12, 13, 15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Amendment and Applicant's Arguments/Remarks filed 11/17/04 is acknowledged.

Claims 8-13, 15 and 16 are pending. Claims 8-10, 12 and 15 have been amended. Claim 14 has been cancelled. Claims 1-7 have previously been cancelled. Claims 8-11 are rejected. Claims 12, 13, 15 and 16 are objected to.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.* (US Pat. No. 5,858,280) in view of Pinchuk *et al.* (US Pat. No. 5,804,318).

Zhang *et al.* teach a method for preparing methyl-modified silica gel using the sol-gel technology, and teach that the modified silica gel produced by the method of the invention have a three-dimensional network structure, which allows doping optically functional substances in high concentrations (see col. 2, lines 10-67).

According to Zhang et al., a methyltrialkoxysilane, such as methyltriethoxysilane, may be combined with a tetraalkoxysilane, such as tetraethoxysilane, or a dialkoxysilane, such as dimethyldiethoxysilane, to control the size and polarity of spaces defined by the polysiloxane network (col. 3, lines 1-15).

Thus, with respect to the compositions claimed in claims 8-10 of the instant application, the prior art discloses modified silica gels obtained from a sol-gel and comprising a tetraalkoxysilane and an alkyl-substituted alkoxysilane, as claimed in claim 8, and a biologically active agent, wherein the tetraalkoxysilane is tetraethoxysilane, as claimed in claim 9, and the alkyl-substituted alkoxysilane is methyltriethoxysilane, as claimed in claim 10.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Zhang et al. is deficient in the sense that the patent does not provide heparin or a related acidic polysaccharide in the gel compositions of the invention and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the prior art teaches that the size of space defined by the polysiloxane network of the invention is particularly suitable to dope optical agents in high concentration (see col. 2, line 58 to col. 3, line 15), thus the patent provides the general teachings that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

With regard to the limitation in claim 8, that a carrier is a xerogel, Zhang et al. does not define the gels of the invention as xerogels, however, the patent contemplates drying the gel, as it teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (col. 2, lines 48-51). A xerogel is a dry polymerized gel, thus the patent contemplates producing silica xerogel carriers, as claimed by Applicant.

Zhang et al. is deficient in the sense that the patent does not provide heparin or a related polysaccharide in the gel compositions and methods of the invention. Additionally, with respect to claim 11, the patent fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant.

Pinchuk et al. provides a hydrogel coating bondable to an epoxy-finctionalized surface of a medical device and comprising anti-thrombogenic agents (see col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (col. 2, liens 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin.

Thus, with regards to claims 8 and 11 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk et al. provides hydrogels comprising 2% heparin. The patent is deficient in the sense, that the reference fails to disclose an amount of 5-30%, calculated on the air-dried xerogel, as claimed by Applicant. Zhang et al. contemplates drying the gel, as

the reference teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (see col. 2, lines 48-51). A xerogel is a dry polymerized gel. It is the view of the Examiner that during the process of air-drying, the gel loses water and concentration of the solutes in the gel increases as a result of the water loss. Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk et al. in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the gel compositions and method for producing said compositions disclosed by Zhang et al., by including heparin in the gel compositions of the invention, as taught by Pinchuk et al., to obtain a composition for the controlled release of heparin and a successful method for preparing said composition. Because of the teachings of Zhang et al., that the gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are useful as carriers for biologically active agents and are resistant to drying, and the teachings of Pinchuk et al., that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would have a reasonable expectation that the compositions claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncova et al. (Collect. Czech. Chem. Commun.) in view of Pinchuk *et al.* (US Pat. No. 5,804,318).

The paper by Kuncova et al. discloses xerogels prepared using sol-gel procedures by hydrolysis of silicon alkoxides (see Abstract and p. 1573), and specifically includes tetraethoxysilane (TEOS), methyltriethoxysilane (METES) and dimethyldiethoxysilane (DMDES) among the alkoxides used in the research (See Solutions IV in Table 1, p. 1574). Thus, with respect to the carrier claimed in claims 8-10 of the instant application, the prior art provides xerogels derived from sol-gels and comprising tetraethoxysilane and alkyl-substituted alkoxysilanes, specifically methyltriethoxysilane and dimethyldiethoxysilane, as claimed by Applicant.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Kuncova et al. are deficient in the sense, that the paper does not provide heparin or a related acidic polysachharide in the xerogel compositions and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the piror art teaches that lipase, a biologically active agent, is immobilized in xerogel compositions and retain its activity for an extended period of time (see pp. 1574-1576 and Table 2). In particular, the reference teaches that the xerogel formed from solution IV, comprising TEOS and DMDES, is characterized by a higher activity of lipase as compared to other xerogels obtained from compositions not comprising the tetraethoxysilane or the alkyl-substituted alkoxysilane (see p. 1574, Table 1 and Table 2). Thus, the prior art provides the general teachings that xerogels

formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

Pinchuk et al. provides a hydrogel coating bondable to an epoxy-finctionalized surface of a medical device and comprising anti-thrombogenic agents (see col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (col. 2, liens 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin. Thus, with regards to claims 8 and 11 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk et al. provides hydrogels comprising 2% heparin (see Example 3). The patent is deficient in the sense, that the reference fails to disclose an amount of 5-30%, calculated on the air-dried xerogel, as claimed by Applicant. Zhang et al. contemplates drying the gel, as the reference teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (see col. 2, lines 48-51). A xerogel is a dry polymerized gel. It is the view of the Examiner that during the process of air-drying, the gel loses water and

concentration of the solutes in the gel increases as a result of the water loss. Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk et al. in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the gel compositions disclosed by Kuncova et al., by including heparin in the gel compositions of the invention, as taught by Pinchuk et al., to obtain a composition for the controlled release of heparin. The expected result would have been a successful gel composition for the controlled release of heparin. Because of the teachings of Kuncova et al., that xerogel compositions prepared using sol-gel procedures by hydrolysis of silicon alkoxides, specifically TEOS, METES and DMDES, are useful carriers as biologically active agent, and the teachings of Pinchuk et al., that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would have a reasonable expectation that the compositions claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 12, 13, 15 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed 11/17/04 have been fully considered and were found persuasive with regards to method claims 12, 13, 15 and 16.

Firstly, Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 8-16 over Zhang et al. (US '280) in view of Pinchuk et al. (US '318) stating, "Page 3 of the Office Action argues that Zhang et al. discloses a biologically active agent...and the Office Action argues that Zhang et al. teach that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.... the Patent Office is requested to cite the column/line number where each disclosure appears".

It is the position of the Examiner that there is no criticality observed in the claimed biologically active ingredient. Admittedly, while Zhang et al. do not teach the instant active agent, heparin, Pinchuk et al. remedies this deficiency of Zhang et al. and is cited for their teaching of a biologically active agent, particularly, heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions. Pinchuk et al. teach that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). Example 3 further demonstrates an epoxy-functionalized silane-primed catheter being dipped into a hydrogel solution comprising 2% heparin. Moreover, it would have been deemed obvious to one of ordinary skill in the art at the time of the invention to employ any suitable active ingredient, based on the desired or intended outcome. The prior art teaches biologically active agents, which include antithrombogenics such as heparin, in hydrogel formulations. The prior art also suggests that the size of space defined by the polysiloxane network of the invention is

particularly suitable to dope optical agents in high concentration (see col. 2, line 58 to col. 3, line 15), thus based on this teaching, the patent provides the general concept that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents. With regards to the instant term 'replaced' in claim 8, the term appears to permit a mixture of a tetralkoxysilane and an alkyl-substituted alkoxysilane. Zhang et al. teach a mixture at column 2, line 58 – col. 3, line 15. Given this teaching, it appears that the prior art teaches Applicant's xerogel.

Secondly, Applicant argued, "The cited combination of references fails to raise a *prima facie* case of obviousness against the claimed composition and method. Zhang et al. fails to disclose or suggest a biodegradable silica xerogel composition, which can be used for the controlled release of a biologically active agent. Instead, Zhang et al. teaches a transparent silica gel, useful as a host material for doping optically functional molecules. There is no indication that the Zhang et al. transparent silica gel is biodegradable. One of ordinary skill in the art would know that residual silanol groups in the xerogel composition are responsible for biodegradability. Zhang et al. teaches an optional heat treatment which will eliminate such residual silanol groups (col. 5, lines 3-21)."

Applicant's arguments have been considered, but were not found persuasive with regards to the composition being claimed. The argument that 'there is no indication that Zhang et al's silica gel is biodegradable' is not persuasive since Applicants have not established that the presence of metal in the silica gel of Zhang et al. would render the silica gel not biodegradable. Still further, as the Applicant admits, the heat treatment step in Zhang et al. is an *optional* step, which therefore implies that in the absence of the heat treatment step, the elimination of residual

silanol groups will not take place and therefore, biodegradability of the xerogel will not be affected. Based on the combined teachings of the references, a *prima facie* case of obviousness has been established.

Next, Applicant argued, "Pinchuk et al. also fails to disclose or suggest that an antithrombogenic agent such as heparin can be encapsulated into sol-gel derived xerogel derived from tetraalkoxysilane which has been co-hydrolyzed with an alkylsubstituted alkoxysilane, or that heparin may be controllably released from the xerogel. The coating itself of Pinchuk et al. is not made of sol-gel derived silica xerogel derived from tetraalkoxysilane. There is no teaching or suggestion that heparin may be controllably released from a sol-gel derived silica xerogel derived from tetraalkoxysilane."

Applicant's arguments have been considered, but were not found persuasive. Pinchuk et al. at column 5, lines 15-21 teaches that the bond between heparin and the hydrogel is ionic and the *heparin slowly releases with time* into the surrounding body fluids to prevent localized clotting. Pinchuk et al. clearly demonstrate that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin.

Lastly, Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 8-11 over Kuncova et al. (Collect. Czech. Chem. Commun.) in view of Pinchuk et al. (US '318) stating, "A feature of the claimed biodegradable composition is the partial replacement of a tetraalkoxysilane with an alkylsubstituted alkoxysilane. Kuncova et al. fails to disclose the partial replacement of a tetraalkoxysilane with an alkylsubstituted alkoxysilane. Pinchuk et al. merely discloses a non-silica hydrogel bound to a surface to be coated by a silane coupling agent."

Applicant's arguments have been considered, but were not found persuasive. Kuncova et al. teach xerogels prepared using sol-gel procedures by hydrolysis of silicon alkoxides (see Abstract and p. 1573), and specifically includes tetraethoxysilane (TEOS), methyltriethoxysilane (METES) and dimethyldiethoxysilane (DMDES) among the alkoxides used in the research (see Solutions IV in Table 1, p. 1574). The prior art provides xerogels derived from sol-gels and comprising tetraethoxysilane and alkyl-substituted alkoxysilanes, specifically methyltriethoxysilane and dimethyldiethoxysilane, as claimed by Applicant. Applicant's argument that 'Kuncova et al. fails to disclose partial replacement of a tetraalkoxysilane with an alkylsubstituted alkoxysilane' is not persuasive since the instant term 'replaced' appears to permit a mixture of a tetralkoxysilane and an alkyl-substituted alkoxysilane. Given this teaching, it appears that the prior art teaches Applicant's xerogel. Therefore, the instant invention is rendered *prima facie* obvious over the teachings of the cited art of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

H. N. Sheikh H.N.S.

Patent Examiner

Art Unit 1615

March 01, 2005

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